IMPROVING MEDICAL AND COSMETIC OUTCOMES IN ACTINIC KERATOSES

Proceedings from a Clinical Roundtable

FACULTY CHAIR
Howard I. Maibach, MD
University of California, San Francisco

CONSEQUENCES OF PHOTODAMAGE: ACTINIC KERATOSIS ETIOPATHOGENESIS
Anthony A. Gaspari, MD
University of Maryland School of Medicine
Baltimore

LESION-TARGETED VERSUS FIELD THERAPY FOR ACTINIC KERATOSES
James M. Spencer, MD, MS
Mount Sinai Medical Center
New York

ACTINIC KERATOSIS IN THE IMMUNOCOMPROMISED HOST
Richard Allen Johnson, MD
Massachusetts General Hospital
Boston

OPTIMIZING PATIENT COMPLIANCE AND COMFORT WITH IMMUNE RESPONSE MODIFIER THERAPY
Phoebe Rich, MD
Private Dermatology Practice
Portland

PREVENTION AND TREATMENT OF SUN DAMAGE: PRESERVING COSMETIC INTEGRITY
Leslie S. Baumann, MD
University of Miami

Produced in affiliation with the 28th Annual Hawaii Dermatology Seminar.
Improving Medical and Cosmetic Outcomes In Actinic Keratoses

4 Consequences of Photodamage: Actinic Keratosis Etiopathogenesis
Anthony A. Gaspari, MD

6 Lesion-Targeted Versus Field Therapy for Actinic Keratoses
James M. Spencer, MD, MS

9 Actinic Keratosis in the Immunocompromised Host
Richard Allen Johnson, MD

11 Optimizing Patient Compliance and Comfort With Immune Response Modifier Therapy
Phoebe Rich, MD

13 Prevention and Treatment of Sun Damage: Preserving Cosmetic Integrity
Leslie S. Baumann, MD

16 CME Post-Test and Evaluation

FACULTY

Howard I. Maibach, MD
Chair
Professor of Dermatology
Department of Dermatology
University of California
San Francisco

Leslie S. Baumann, MD
Director, Division of Cosmetic Dermatology
Associate Professor
Department of Dermatology
University of Miami

Anthony A. Gaspari, MD
Professor of Dermatology
Department of Dermatology
University of Maryland
School of Medicine
Baltimore

Richard Allen Johnson, MD
Instructor in Dermatology
Harvard Medical School
Clinical Associate in Dermatology
Massachusetts General Hospital
Boston

Phoebe Rich, MD
Clinical Professor of Dermatology
Oregon Health Sciences University
Private Dermatology Practice
Portland

James M. Spencer, MD, MS
Vice Chairman and Associate Professor
Department of Dermatology
Mount Sinai Medical Center
New York
CME RECOGNITION
Skin & Allergy News certifies that this educational activity has been recognized for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology’s Continuing Medical Education Award. This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.
TERM OF APPROVAL: January 2004 - December 2004

TARGET AUDIENCE
This activity has been developed for dermatologists and other health care professionals involved in the diagnosis, treatment, and long-term management of patients with actinic keratoses (AKs).

EDUCATIONAL NEEDS
Long-term ultraviolet (UV) radiation from the sun and tanning salons is now known to result in photodamage to the skin that has both medical and cosmetic consequences. New findings from basic scientific research have provided information that is crucial to the understanding of the process of photodamage and photoaging on biochemical and genetic levels. In addition, clinical studies have explored the efficacy and safety of a range of treatments for actinic keratoses. Dermatologists must be kept up-to-date on these findings to be able to advise patients about the latest information on prevention of photodamage and photoaging and to guide them through informed choices about treatment.

LEARNING OBJECTIVES
By reading and studying this supplement, participants should be able to:
• Discuss the most recent findings in basic scientific research that explain how ultraviolet radiation affects skin cells to produce actinic keratoses and manifestations of aging, such as wrinkling.
• Summarize the modalities currently available for the treatment of AKs, including immune response modifier therapy, and list the major advantages and disadvantages of each.
• Describe what is currently known about actinic keratoses and invasive squamous cell carcinoma in immunocompromised patients.
• Explain the newest findings concerning the pathways of photoaging and the methods for blocking these pathways.

FACULTY DISCLOSURES
Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr. Baumann discusses the investigational use of imiquimod for the treatment of actinic keratosis.
Dr. Gaspari has received a research grant from and is on the Medical Advisory Board of 3M Pharmaceuticals. He discusses the investigational use of imiquimod for the treatment of actinic keratosis and basal cell carcinoma.
Dr. Johnson discusses the investigational use of actretin, adapalene, imiquimod, tazarotene, and tretinoin for the prevention of actinic keratosis and squamous cell carcinoma in organ transplant recipients. He also discusses the investigational use of isotretinoin for the treatment of xeroderma pigmentosum. Dr. Maibach has nothing to disclose. Dr. Rich has received funding for clinical grants from and is a consultant to 3M Pharmaceuticals. She discusses the investigational use of imiquimod for the treatment of actinic keratosis. Dr. Spencer has received funding for clinical grants from 3M Pharmaceuticals and ICN Pharmaceuticals, Inc. He is a consultant to and has a financial interest in PhotoMedex. He discusses the investigational use of imiquimod for the treatment of actinic keratosis.
Actinic keratosis (AK) has been a relatively neglected research and clinical topic. This supplement provides some of the research information, such as the relationship of c-Fos and c-Jun to this clinical problem.

Topical 5-fluorouracil for the treatment of AKs was developed after the empiric observations of the late C. Dillaha at the University of Arkansas Medical School. No other American approvals for AK treatments occurred until the introduction of masoprocol, which remained available briefly in the United States.

Health care providers are currently being updated on numerous therapies for AK, including photodynamic therapy (two agents in Europe and one in the United States) and imiquimod. A panel of distinguished faculty were assembled to review what is known about the nature of AK as well as evidence-based and anecdotal experience related to treatment of AK lesions.

Anthony A. Gaspari, MD, addresses the current theory concerning the role of ultraviolet light damage. James M. Spencer, MD, MS, describes when lesion-targeted treatment is indicated and when field therapy is preferred. Richard Allen Johnson, MD, discusses the unique problem that AKs present for solid organ transplant recipients and other immunocompromised hosts. Phoebe Rich, MD, presents a perspective on AK treatment with an immune response modifier, stressing strategies for titrating the dosage to improve patient comfort and compliance. Finally, Leslie S. Baumann, MD, explains recent findings regarding the nature and prevention of photoaging.

In sum, these articles present a succinct introduction to current advances and a hint as to a rapidly evolving paradigm in AK therapy.

—Howard I. Maibach, MD

Consequences of Photodamage: Actinic Keratosis Etiopathogenesis

Anthony A. Gaspari, MD

Actinic keratosis (AK), once considered only a benign cosmetic problem, is now recognized as an indicator of photodamage, and AK lesions are possible precursors to squamous cell carcinoma (SCC). Indeed, the emerging view is that AKs are precursor lesions for nonmelanoma skin cancer (NMSC), which may or may not progress to invasive SCC.

In the United States, 200,000 new cases of SCC are diagnosed yearly, and several papers have estimated the number of AKs that progress to SCC. These estimates range from less than 1% to 16%, but it must be noted that a standardized, uniform method to predict which AKs will progress to SCC has not been developed. Further, lesion counts often vary among observers, and studies of AKs differ in their methodologies and the duration of follow-up. Therefore, the accuracy of any estimate of incidence and rate of progression is questionable, at best.

Clinical Presentation

The clinical presentation of AKs is well-known to dermatologists, so only a brief review is needed here. AKs, sometimes referred to as solar keratoses, are red-brown macules, papules, or plaques with dry scale and ill-defined boundaries. These lesions range in size from barely visible to 3 mm in diameter, occasionally larger, but most of those that are clinically identifiable are between 1 and 3 mm. AKs often are easier to detect on palpation than on visual inspection. However, an estimated threefold to tenfold greater number of lesions are present than can be appreciated on physical examination, either by inspection or palpation.

AKs most frequently occur on sun-exposed areas of the body, most commonly on the upper limbs, face, scalp, ears, and neck. The risk factors for AK that have been identified to date include a cumulative lifetime history of sun exposure, a genotype indicating sun sensitivity (fair skin, blue or green eyes, etc.), and a history of nonmelanoma skin cancer or AKs. The newest addition to this list is immunosuppression. Individuals who are undergoing cancer chemotherapy or posttransplantation immunosuppressive treatment, or who have disorders or diseases of the immune system are now recognized to be at increased risk for AKs and aggressively progressive SCC.

Multiple Steps in Progression of NMSC

According to the current theory, two major damaging events occur as a result of cumulative ultraviolet (UV) light exposure from natural sunlight or tanning salons. The greatest adverse effects have been associated with shorter wavelengths of UV light—that is, UVB light—in the range of 290 to 320 nm, but UV damage also is associated with longer UV wavelengths—UVA light—in the range of 320 to 400 nm. One of the two major damaging events from UV light is a series of mutations in critical genes of epidermal keratinocytes. The second is the direct and indirect effects of UV light on the skin’s immune system, which results in a defect in immune surveillance. The combination of these two events allows UV-induced skin tumors to emerge over time.
Damage to Epidermal Keratinocytes

One critical gene affected early in both AK and SCC is the so-called guardian of the genome, p53. When the p53 gene functions normally, it detects damage to the DNA in a cell and triggers programmed cell death, apoptosis. However, when UV-induced mutations cause defects in the p53 gene, cells with a damaged genome fail to undergo apoptosis. Another critical set of genes that can be affected by UV light exposure is the family known as ras oncogenes. These genetic changes result in the development of premalignant clones that have an enhanced survival advantage. With further accumulation of UV light exposure, a clonal expansion of these cells occurs, and the result can be manifested clinically—or subclinically—as AK (Figure).5,10

Additional UV light exposure can lead to the accumulation of other genetic abnormalities in the affected cells that prompt progression along the continuum from sun damage to AK to SCC. These include increasing expression of genes associated with proliferation, such as Ki-67 and proliferating cell nuclear antigen. Also increasingly expressed in these damaged cells are genes such as telomerase and survivin, which are associated with cell survival and replication as well as the inhibition of senescence. At the same time, expression of genes that control terminal differentiation and apoptosis is decreased. Other genes that control T-cell–induced survival, immune recognition, and apoptosis—that is, the mechanism by which T cells attack a tumor—progressively are downregulated, as premalignant keratinocytes progress toward SCC.

Damage to Skin Immune System

During this molecular and cellular progression from the premalignant clone to an initiated and promoted clone and then to frank SCC, the immune system has an opportunity to recognize and eliminate these premalignant or even malignant clones. The failure of the immune system to eliminate these affected cells is related to the deleterious effects of UV light on the skin’s immune system.

The central cell type affected by UV light is the epidermal Langerhans’ cell. The Langerhans’ cell can activate the subset of helper T cells known as Th1 (which produce interferon-γ after activation by antigen-presenting cells such as Langerhans’ cells). However, it has been demonstrated that after UV light damage, Langerhans’ cells are deficient in this particular T-cell host defense, antigen-presenting pathway.11 Instead, the UV-irradiated Langerhans’ cells tend to activate helper T cells type 2 (Th2), which produce interleukin (IL) 4, in turn resulting in excessive activation of suppressor T cells.12

The weak Th1 response against potential tumor antigens and the dominant suppressor cell effect yield the net effect of an immune system that is tolerant to antigens expressed by tumor cells. In effect, the skin’s immune system is paralyzed and is unable to effectively mount a response to eliminate initiated and progressing cells that are on their way from AK to full-blown SCC.

UV light directly kills Langerhans’ cells in the epidermis.13 The few Langerhans’ cells that survive are exposed to a number of soluble immunosuppressive mediators that are derived from UV-irradiated epidermal keratinocytes. These factors, including IL-10,14-17 tumor necrosis factor, prostaglandins,19 and urocanic acid,19 further damage the surviving Langerhans’ cells and deplete their ability to respond effectively to evolving tumor antigens.12,14

Molecular and Biochemical Consequences of Photodamage

Comparative studies of sun-damaged skin, AK, and SCC indicate that these three are related and represent a continuum from early initiated clones of keratinocytes with UV damage to critical tumor suppressor genes such as p53 to intermediate stages of tumor promotion and fully malignant SCC.

As abnormal cells make the transition from UV-damaged, precancerous, clonal lesions—that is, AKs—to malignant SCC with aggressive, invasive biologic activity, a progressive accumulation of genomic mutations occurs, including loss of tumor suppressor genes and activating mutations to protooncogenes such as ras. In addition, chromosomal abnormalities, loss of cell cycle control, cytokine dysregulation, and resistance to apoptotic stimuli occur.20

DNA Repair Capacity

DNA repair of UV light damage to the genome of epidermal keratinocytes represents an innate defense mechanism in the pathogenesis of NMSC.21 Studies of patients with the rare genetic disorder xeroderma pigmentosum have confirmed the correlation of diminished DNA repair of UV light damage to the markedly increased susceptibility to skin cancer development at an early age.22 There is evidence that skin cells progressively lose their capacity to repair DNA damaging with aging.23,24 This observation supports the concept that increasing num-

Continued on page 15
Lesion-Targeted Versus Field Therapy for Actinic Keratoses

James M. Spencer, MD, MS

Actinic keratoses (AKs) are lesions commonly diagnosed in a dermatology practice. There are two types of approaches to the management of AKs: destructive modalities and medical therapies. All of the destructive modalities, except for resurfacing procedures, are lesion-targeted treatments and may be considered for eradicating isolated, discrete lesions. Resurfacing procedures and medical therapies are classified as field therapy, appropriate for treating multiple AKs in an anatomic region.

Destructive Modalities

The most commonly used treatments for AKs are destructive modalities—that is, those in which a physical modality is employed to produce cell death in the AK while, ideally, sparing the surrounding normal structures. The destructive modalities include cryosurgery, curettage with or without electrodesiccation, electrodesiccation alone, shave excision, and surgical excision.

Cryosurgery

Cryosurgery probably is the most common treatment for AKs in the United States today. Many cryogens are available to lower the temperature of the skin, but liquid nitrogen is used most frequently.

For the treatment of most AKs, a very brief freeze—1 to 3 seconds—is adequate to destroy the target keratinocytes in the epidermis. The required depth of the freeze is only 0.1 to 0.2 mm, and creation of a dermal wound, marked by vesiculation, is not necessary. AKs that are moderately to severely hyperkeratotic often are resistant to this less aggressive method of liquid nitrogen treatment, but a deeper freeze is associated with an increased risk for scarring and/or hypopigmentation. In such cases, if liquid nitrogen is the treatment of choice, the more conservative—and cosmetically safer—approach is to use a single, brief freeze and to have the patient return for an additional treatment if the AK has not completely resolved.

To determine the depth of a liquid nitrogen freeze, consider the formation of the crystals on the surface of the skin. The circle of white area that forms on the surface should be thought of as one plane in a sphere, such that the lateral extent is equal to the vertical extent.

Cryosurgery is widely held to be highly effective, although this is a poorly documented belief. A literature search revealed a single paper, published by Lubritz and Smolewski in 1982,1 which attempted to establish the efficacy of cryosurgery in AKs. In this retrospective review of 70 patients who had undergone cryosurgery for 1,018 AKs, the investigators reported a 98% cure rate. The patients were followed clinically for 1 to 8.5 years. Although the follow-up methodology could not be described as strict, most practicing dermatologists would agree that cryosurgery is highly effective.

Curettage

Curettage has the advantage of removing an AK while providing a sample for histologic analysis. This is the best option when it is unclear whether an AK lesion has progressed to an invasive squamous cell carcinoma (SCC). Electrodesiccation following curettage provides hemostasis and may provide a bit of a wider range of tissue destruction than that which occurs with curettage alone. (Electrofulguration, however, does not produce as much additional tissue destruction as one might imagine, creating instead a superficial eschar.) The true efficacy of curettage, with or without electrodesiccation, has not been established in controlled studies, but, as with cryosurgery, the long-term clinical experience of countless dermatologists suggests that it is highly effective.

Shave excision, like curettage, is another method of preserving tissue for pathologic study. Full-thickness excision is reserved for cases in which malignancy is strongly suspected. Again, controlled studies are lacking with these methods, but it is reasonable to assume high efficacy.

Resurfacing Procedures

Resurfacing procedures are highly controlled destructive techniques that are appropriate for managing multiple AKs in a given anatomic region. The advantage of resurfacing procedures over the destructive modalities discussed above is that they create a controlled wound and are associated with a higher safety profile and less incidence of scarring. These procedures include a medium-depth chemical peel with trichloroacetic acid, a deep chemical peel with phenol, dermabrasion, and resurfacing with either carbon dioxide or erbium yttrium aluminum garnet laser.

Weighing the Options

When a patient has an isolated, discrete lesion that is clearly visible, destructive therapies are without question the most popular choice. Although cryosurgery is moderately uncomfortable, no anesthesia is required, but because of the sensitivity of melanocytes to freezing, hypopigmentation is not an uncommon sequela. Patients with any AKs have sustained sufficient photodamage to develop more lesions over time, so multiple cryotherapy treatments in the same area would leave
a cosmetically undesirable "white checkerboard" appearance. Curettage, electrodesiccation, shave excision, and full-thickness surgical excision require local anesthesia, and all of these procedures are very likely to produce scarring.

All of the resurfacing procedures discussed remove the epidermis within an entire field, achieving the goal of eliminating AKs at all stages, including subclinical lesions. The disadvantages include "downtime" for the patient during the healing process and the associated risk for infection and scarring. In addition, all of these modalities are expensive and are considered to be cosmetic (and not reimbursed by health insurance). Finally, for safety and optimum cosmetic results, these methods all require extensive training, experience, and expertise on the part of the clinician.

MEDICAL THERAPIES
The current theory of AK etiopathogenesis is that these lesions are clonal and, thus, originate from a single cell. The changes that produce AK can occur concurrently in separate cells within a single anatomic area, producing multiple, separate, simultaneously occurring lesions—the phenomenon known as "field cancerization." Multiple lesions in a single area will be in various stages of development at any given point in time. Among these will be lesions too small to detect clinically, and with destructive therapies it is not possible to treat what cannot be seen. Further, the risk for hypopigmentation and scarring on multiple lesions makes the use of almost all of the destructive treatments on cosmetically sensitive areas—such as the scalp (Figure), face, and neck—unacceptable to most patients.

Therefore, when confronted with multiple lesions within an anatomic region, it is best to treat the entire area. The ideal treatment should be safe, well tolerated, and not permanently disfiguring. In addition, it should treat visible and subclinical lesions in a large area and produce a pleasing cosmetic outcome. Several medical therapies are currently available and are briefly reviewed here.

5-Fluorouracil
5-Fluorouracil (5-FU), most commonly prescribed at a concentration of 5%, has been popular for the treatment of AKs. Because 5% 5-FU was marketed prior to the establishment of the requirement for phase III clinical trials, no randomized, double-blind, controlled trials have been conducted with this formulation. Some uncontrolled trials suggest that 5% 5-FU’s efficacy is about 75%. The disadvantage with the use of 5% 5-FU is that it can cause significant discomfort and temporary disfigurement. This is a particular problem when the face and scalp are being treated, both because of the sensitivity of the areas and because of the cosmetic appearance during treatment.

Currently, 5-FU is available in 5% cream and solution, 2% solution, 1% cream and solution, and, more recently, introduced, a 0.5% micronized cream formulation. The micronized formulation was developed in an effort to improve tolerability. An early, small study of less than 1 month comparing 5% and 1% 5-FU in 16 patients demonstrated that the formulations were equivalent in clearing AKs. In a single-blind, randomized, split-face study comparing 0.5% micronized 5-FU cream with 5% cream, Loven and colleagues found that the formulations were equally effective in reducing the percentage of AKs, but the majority of participants in this study (P=0.003) said they found the micronized formulation more tolerable.

Diclofenac
Another choice for medical therapy is diclofenac in hyaluronic acid. Diclofenac is a nonsteroidal antiinflammatory drug that is now available commercially in topical form for the treatment of AKs. Wolf and coworkers conducted a randomized, double-blind, placebo-controlled trial in which 120 patients used the active drug for 90 days. Forty-seven percent of patients in this group had complete clearance of visible lesions, compared with 19% of those in the placebo group (P<0.001). Note that no significant difference in improvement was found before 90 days of treatment.

In this study, diclofenac was generally well tolerated, with only mild cutaneous side effects. Vesicles and ulcerations were rare. The major benefit compared to that with 5-FU is that diclofenac produces minimal inflammation. However, efficacy is not as great and the treatment period is about three times as long—3 months for diclofenac, compared with 2 to 6 weeks for 5-FU, depending on the formulation and dosage schedule.

Retinoids
The topical retinoid tretinoin has been shown in several studies to be effective in eliminating approximately 50% of AKs over a period of 6 months or longer. This is a chronic treat-
ment that can be considered as long-term even lifelong maintenance therapy for patients who are at high risk for developing multiple AKs that are likely to progress to SCC.

**Photodynamic Therapy**

Photodynamic therapy (PDT) with 20% aminolevulinic acid (ALA) and a blue light source was introduced in the United States in 1999 as a treatment for AKs. ALA preferentially accumulates in dysplastic and malignant cells where it is converted enzymatically to protoporphyrin IX, a potent photosensitizer. The agent is applied to visible AKs at one office visit, and the patient returns the next day for completion of the procedure. In response to the light source, reactive oxygen species are generated, resulting in oxidative damage and death of the targeted cells.

Jeffes and colleagues described the efficacy of PDT in a multicenter, investigator-blinded, randomized, vehicle-controlled study of 36 patients with nonhyperkeratotic AKs of the face and scalp. At the optimal light dose of 10 J/cm², 88% of AKs had cleared completely 8 weeks after one treatment. In contrast, only 6% of lesions cleared in the patients who received vehicle and light.

PDT requires two office visits, and a study by Kurwa and coworkers suggests that it is as effective as 5% 5-FU and yields the same subjective reports from patients of erythema and pain. Currently, clinical trials are under way, testing techniques to minimize side effects and to make PDT more convenient (allowing the treatment to be completed in only one office visit).

**Imiquimod**

Topical imiquimod is an immune response modifier that works by eliciting local cytokines, including interferon-α, interferon-β, and interleukin-12. Imiquimod has been demonstrated to stimulate both nonspecific (interferons and natural killer cells) and specific (T cells) immune responses. Based on the observation that intralesional administration of interferon was effective in eliminating AKs, investigations have been conducted to determine whether elicitation of an immune response by imiquimod would be effective in the treatment of AKs.

Recently, Persaud and colleagues treated 22 patients with imiquimod on one side of the body and vehicle cream on the other, three times a week for 8 weeks or until total clearance of the lesions was achieved. Seventeen patients completed the treatment, and the investigators reported a significant reduction in the average number of lesions per patient treated with imiquimod therapy. The most common side effects reported were mild to moderate erythema, itching, and scabbing. The investigators did allow rest periods if significant inflammation developed, and when the reaction resolved sufficiently, patients resumed treatment at a lower dosing frequency: nine used imiquimod twice weekly, and four patients decreased applications to once weekly. Thus, it appears that topical imiquimod can be titrated to tolerability and still be effective.

In Germany, Stockfleth conducted a placebo-controlled trial in 36 patients with AKs, 25 of whom received imiquimod and 11 of whom served as controls. The medication was applied three times a week for 12 weeks. Twenty-one of the patients in the imiquimod group were completely cleared and two were partially cleared, a clinical observation that was confirmed by biopsy. Interestingly, during the course of the study, 12 patients decreased imiquimod dosing frequency to twice weekly, and one patient decreased applications to once weekly, yet these patients achieved the best results.

The tentative conclusion that can be drawn from these two studies is that imiquimod applied three times weekly is effective for the treatment of AKs, but if significant inflammation develops, dosing can be titrated to tolerability without loss of efficacy.

**Conclusion**

In some cases in which multiple lesions are present, treatment with a single modality may not be adequate to clear all lesions. My approach with such difficult patients is to treat first with a medical modality to clear as many lesions as possible. Persistent lesions may then be dealt with using one or more destructive methods. In addition, if the appearance of any of the remaining lesions suggests the presence of malignancy, the clearer field allows a biopsy to be targeted to just the suspicious-looking area.

**References**

3. Loven K, Stein L, Forsk K, Levy S. Evaluation of the efficacy and tolerability of 0.5% fluorouracil cream and 5% fluorouracil cream applied to each side of the face in patients with actinic keratoses. Clin Ther. 2002;24:990-1000.
Actinic Keratosis in the Immunocompromised Host

Richard Allen Johnson, MD

Individuals with human immunodeficiency virus (HIV) infection, numbering more than 800,000, according to the most recent figures available from the U.S. Centers for Disease Control and Prevention, represent perhaps the largest population of immunocompromised patients in the United States today. In addition, an estimated 140,000 Americans are currently living with transplanted organs and undergoing immunosuppressive therapy, and 23,000 organ transplant procedures are performed each year. A number of dermatologic procedures are performed each year.2 A number of dermatologic conditions, including albinism, xeroderma pigmentosum, lymphocytic leukemia or lymphoma (possibly as a result of T-cell decline), are associated with decreased immunocompetence. Finally, individuals undergoing chemotherapy are iatrogenically immunosuppressed. Nonmelanoma skin cancer (NMSC)—particularly squamous cell carcinoma (SCC)—is a risk in all of these populations, either because of an increased incidence or because the cancer is more aggressive.

Patients Living With HIV/AIDS

With the advent of highly active antiretroviral therapy, patients infected with HIV can live for years or decades after their diagnosis. It has been my clinical experience that those with a long-term history of chronic ultraviolet (UV) light exposure can be expected to develop many actinic keratoses (AKs) and, subsequently, invasive SCCs. This is poorly documented. Although it seems that patients with HIV/acquired immunodeficiency syndrome (AIDS) do not have an increased incidence of SCC, those in whom SCC does develop apparently have an aggressive course and an increased risk for death within a short time.

Nguyen and colleagues3 recently published a retrospective, nonrandomized case series of 10 patients with HIV disease. The mean age of onset of SCC was 44 years. Although these patients received treatment, five died from metastatic SCC within 7 years of diagnosis. The patients who died had not been treated aggressively initially with surgery plus radiation therapy or surgery and radical neck dissection.

In my own practice, I have seen two patients with HIV who developed SCC. In one of them, a 48-year-old white man, a 1-cm SCC arose on the left scalp and grew rapidly in 1 month (Figure). The patient died 1 month thereafter of metastatic SCC.

Organ Transplant Recipients

In the general population, the ratio of SCC to basal cell carcinoma (BCC) is 1:4, but in patients who are immunosuppressed following organ transplantation, the ratio is reversed, and the ratio of SCC to BCC is 4:1. The most common cause of death 5 years after transplantation is metastatic SCC.4

Immunosuppressive drugs administered both acutely and as long-term maintenance therapy following transplant surgery may accelerate the development of skin cancer in transplant recipients by two distinct mechanisms. First, these drugs may be directly carcinogenic. Second, these agents create a state in which immune surveillance and eradication of precancerous lesions are impaired.

The most important risk factor for melanoma and NMSC following organ transplant surgery is sun exposure prior to transplantation. The patients at highest risk for skin cancer are those with skin types I through IV who live in regions closest to the equator. Patients with darker skin types—those of African or Asian heritage, for example—do not appear to be at increased risk. The highest worldwide incidence of skin cancer in transplant recipients has been reported in Australia and New Zealand.5 It would be reasonable to assume that in the United States, a higher incidence would be found among fair-skinned individuals who live in areas such as Florida or Southern California.

Even in more temperate climates, however, the rates of skin cancer in transplant recipients is still high. Data from population-based cohorts in Norway7 and the Netherlands6 show that fair-skinned patients who undergo organ transplantation have a 65-fold increased incidence of cutaneous SCC, a 20-fold increased incidence of SCC of the lip, a 10-fold increased incidence of BCC, and a 3.4-fold increased incidence of melanoma.8 In addition, the incidence of Kaposi’s sarcoma was increased 84-fold in these populations.

Management of Patients After Organ Transplantation

It is important to identify patients at risk, based on the inherent and environmental factors noted, and to monitor them closely for signs of developing skin cancer. Transplant recipients—particularly those with skin types I through IV—should perform self-examination of the skin at least
monthly. In addition, patients should be examined by a dermatologist according to follow-up intervals recommended by Otley:

1. once yearly for patients with no history of skin cancer or AKs, every 6 months for those with AKs or a history of one NMSC lesion, every 2 to 4 months for those with a history of multiple NMSC lesions, every 3 months for those with a history of high-risk SCC or melanoma, and every 2 months for patients with metastatic SCC or melanoma.

All patients should understand that avoidance of UV radiation is crucial for preventing skin cancer posttransplantation. UV light may initiate skin cancer and/or promote the growth of an existing malignant lesion. Exposure to UV radiation suppresses the skin’s immune system, and, in an already immunocompromised host, this can further inhibit antigen presentation and recognition.

Human papillomavirus (HPV) has been identified as a potential cofactor in the development of cutaneous SCC in both immunosuppressed and immunocompetent patients. It is estimated that HPV infection is present in up to 90% of SCCs in organ transplant recipients. HPV types 16 and 18 are considered to be oncogenic. Immunocompromised individuals infected with these HPV types are at higher risk for in situ and invasive SCC on the anogenital epithelium, as well as at other sites such as the nail apparatus.

Chemoprophylaxis

Chemoprophylaxis with retinoids has been used as a strategy for preventing skin cancer in this population because these agents modulate cell proliferation and apoptosis. Isotretinoin, 2 mg/kg, was used in early studies of patients with xeroderma pigmentosum, and although the incidence of skin cancer was reduced, drug toxicity was a problem for some patients, and cessation of therapy was associated with the reappearance of the pretreatment phenotype. Additional studies with low doses of isotretinoin in patients with xeroderma pigmentosum demonstrated no benefit.

Phytophylactic use of systemic retinoids has been studied in transplant recipients. Bavinc and colleagues conducted a small study of renal transplant recipients using 30 mg/day of acitretin. A significant decrease in new SCCs was seen over the 6-month period of the trial: two SCCs developed in 11% of patients receiving acitretin, whereas 18 new SCCs developed in 47% of patients on placebo. A retrospective, 5-year review of renal transplant recipients who received 0.3 mg/kg/day of acitretin following surgery also suggested a significant benefit associated with use of this drug. Most recently, de Sévaux and coworkers published the results of a randomized trial comparing two doses of acitretin in 26 renal transplant recipients. One group of patients received 0.4 mg/kg/day for 12 months; the other group received 0.8 mg/kg/day for 3 months and 0.2 mg/kg/day for 9 months. These investigators found that the number of AKs was decreased by almost 50% in both groups and that the thickness of AKs that did develop was significantly decreased in both groups. The drug did not have any effect, however, on the incidence of new malignancies in either group.

Topical retinoids also may be considered to help prevent the progression of AKs. Several studies have assessed their use specifically in renal transplant recipients as an adjunct to systemic retinoids.

The application of the topical immune response modifier imiquimod has been studied in AKs in immunocompetent patients in the United States with good results, but its efficacy and safety have not been assessed in U.S. studies in organ transplant recipients. Stockfleth and his group in Germany have reviewed the use of newer methods of treatment for preventing skin cancers in organ transplant recipients and note the desirability of enhancement of local immunity by topical therapies. These include the use of retinoids such as tazarotene, adapalene, and tretinoin, as well as imiquimod.

The theoretical concern with activating or modifying the immune response with a topical agent—and, thus, inducing interferon and cytokines locally—is that the risk for rejection of the transplanted organ may be increased. However, there is no evidence that this is a practical concern.

Conclusion

Immunosuppressed individuals with skin phototypes I through IV are at increased risk for morbidity and mortality from cutaneous SCC. The risk is higher in those with the greatest cumulative UV exposure. Treatment of AKs is indicated, using standard medical and surgical methods. Oral or topical administration of retinoids decreases the incidence of invasive SCC. Topically applied imiquimod may restore UV-induced local immunosuppression and may reduce the incidence of NMSC.

References


Continued on page 15
Optimizing Patient Compliance and Comfort With Immune Response Modifier Therapy

Phoebe Rich, MD

When medical therapy is the treatment of choice for a patient with actinic keratoses (AKs), a clinician may determine that immune response modifier therapy is the most appropriate approach for that patient. Clinical studies of the immune response modifier imiquimod have been conducted in an attempt to determine the best schedule for using this agent in patients with AKs. Treatment outcomes with various dosing schedules were part of two recently completed phase III, multicenter, double-blind, placebo-controlled studies of imiquimod in the treatment of AKs. The U.S. Food and Drug Administration has not yet approved imiquimod for the indication of AKs, but an application is pending. The experiences of investigators who conducted smaller clinical trials have been published. In addition to exploring the efficacy of imiquimod, these studies focused on the optimum dosing schedules for its use.

**Cycle Therapy**

Salasche and colleagues studied the efficacy of imiquimod using a cyclic regimen. This consisted of once-daily applications of the cream at night, three times a week for 4 weeks, followed by a 4-week rest period and additional periods of treatment and rest as needed to achieve the desired result. Three cycles were permitted as the maximum.

This open-label trial included 25 patients (23 men, 2 women) with AKs at 33 cosmetic units (13 scalp, 13 forehead, and 7 cheeks). At the end of the first cycle, 15 out of 33 (45%) of the cosmetic units had cleared. At the end of the second cycle, an additional 12 cosmetic units had cleared (36%). By the end of the study, 27 out of 33 (82%) cosmetic units had completely cleared. (In all cases in which complete clearance was seen, this occurred by the end of two cycles.)

Regarding the number of lesions, 368 AKs were counted at baseline, a mean of 11.15 AKs per cosmetic unit. By week 2, the count had increased to 613 (mean, 19 per cosmetic unit); these additional AKs were previously subclinical lesions that had become evident on exposure to imiquimod. At week 4, the total count was 515 (mean, 16 per cosmetic unit), and at 2 weeks into the rest period (or week 6 of the study), the count had dropped to 228 (mean, 7 per cosmetic unit). At the end of the first cycle—that is, after 4 weeks of treatment and 4 weeks of rest—the AK count was 144 (mean, 4.36 lesions per cosmetic unit).

Local skin reactions were mild to moderate. Most of the local skin reactions—erythema, edema, and crusting—occurred in the first cycle.

The three major conclusions concerning cycle therapy were that (1) it was highly effective, (2) it was associated with only mild to moderate local adverse reactions, and (3) as with non-cyclic regimens, subclinical lesions became visible and were cleared.

**Histologic Confirmation of Efficacy**

Stockfleth and colleagues conducted a randomized, double-blind, vehicle-controlled study to assess 5% imiquimod in the treatment of multiple AKs. Subjects applied imiquimod or vehicle to AKs three times a week for a maximum of 12 weeks, or until complete resolution of lesions was achieved. The study protocol included a provision for a reduction in dosing frequency to once or twice weekly if adverse reactions occurred. In addition, rest periods were permitted.

Clinical clearance occurred in 21 of 25 patients (84%), and partial clearance was reported in two others (8%). In all of those whom lesions had resolved clinically, clearance was confirmed histologically 2 weeks after the last application of imiquimod. The investigators reported that there was no change in the size or number of AKs in the patients in the control group.

The adverse effects seen in the treatment group were mild to moderate erythema, edema, induration, flaking, vesicles, erosion, ulceration, excoriations, and scabbing. However, no patient dropped out of the 12-week study because of these skin reactions.

These subjects were evaluated again after 1 year, and 10% of the patients who had experienced complete clearance had AKs at that time.

**Educating Patients About Immune Response Modifier Therapy**

Education about the unique mechanism of action of imiquimod is as important as careful instructions on its application at home. Unless patients understand how imiquimod works, they may become unnecessarily alarmed as subclinical lesions “light up” in treated areas. Patients should be advised to expect at least mild erythema and edema, and informed that where AKs are seen, damage from the sun is likely to have caused other AKs that may not yet be visible (Figure on page 12). They should understand that any inflammation that occurs is a favorable sign because it is an indication that the immune cells in the skin have been activated at the site of imiquimod application to fight and clear the AKs.

Those who experience a robust reaction with moderate or, rarely, severe erythema, edema, and erosions should be reassured that they have not developed an infection but that the treatment is having the desired effects. Patients are advised
to contact our office if they experience discomfort or if weeping or oozing is seen in the treated area.

**Titrating to Tolerability, Managing Side Effects**

Effective treatment for AKs is not a "one size fits all" approach. An isolated lesion is often simply and effectively treated with liquid nitrogen. An alternative is medical therapy with imiquimod or 5-fluorouracil (5-FU) cream.

When patients have mild to moderate actinic disease—that is, multiple lesions in one or more regions rather than a few, discrete, isolated lesions—topical medical therapy with imiquimod, 5-FU, or diclofenac can be options. When imiquimod is the chosen therapeutic modality for AKs, the treatment should be titrated to maximize compliance, comfort, and efficacy.

In my practice, the typical initial protocol for imiquimod therapy of the face is applications every other day until erythema is seen, which indicates activation of subclinical lesions. The medication is applied in a very thin layer at bedtime and left on overnight. Depending on the briskness of the response to treatment, the application schedule is decreased to twice weekly or even once weekly.

For treatment of the chest, back, and hands, we start with applications every other day. If no reaction is seen—which is not uncommon with hyperkeratotic lesions and those that occur on the dorsa of the hands—a regimen of more frequent applications can be used. With such difficult lesions, daily applications may be necessary to achieve a therapeutic response.

Patients return for a follow-up visit after 2 weeks, and those with mild to moderate skin reactions and no undue discomfort are told to continue therapy for an additional 2 weeks before progress is rechecked. Patients with a more intense response are given a 1-week rest period before completing the additional weeks of treatment. If necessary, cycles of treatment are repeated.

Titrating to tolerability is most likely to yield the best results in terms of patient comfort and compliance. Some patients do well with very low frequency of applications, such as once weekly over a longer period of time. It is my experience that the cosmetic and therapeutic outcomes are excellent with these conservative treatment schedules. In order to maximize compliance, efficacy, and patient comfort, the treatment must be explained to the patient and tailored to individual skin type and severity of actinic damage.

In some cases, inflammation persists even after treatment ends. Given imiquimod's known mechanism of action, it is not unreasonable to speculate that this indicates continued activity of the drug at the site of application. Some clinicians prescribe applications of topical corticosteroids in such cases. However, it is a theoretical concern that topical corticosteroids might exert an immunosuppressive effect and decrease the efficacy of any residual response from imiquimod. Instead, moisturizers or emollients can be applied as needed. With careful titration, erosions and ulcerations are not common. If they do occur, a topical antibiotic can be applied until reepithelialization occurs.

**Conclusion**

The physician has many choices for the effective treatment of AKs. When deciding which therapy to recommend, the patient’s lifestyle and needs should be considered and the patient should be informed about the advantages and disadvantages of the various medical and surgical treatment options (see Dr. Spencer’s article, “Lesion-Targeted Versus Field Therapy for Actinic Keratoses,” page 6). If imiquimod is the treatment chosen, cycle therapy, reducing frequency of applications, and allowing rest periods are measures that can be taken that can increase patient comfort and compliance while preserving therapeutic efficacy.

**References**


Recent basic scientific research has yielded much valuable evidence concerning the nature and prevention of photoaging—e.g., two genes are important in the process of photoaging, c-Jun and c-Fos. C-Fos levels in the skin are relatively constant, but the levels of c-Jun fluctuate, increasing on exposure to environmental insults such as ultraviolet (UV) radiation and cigarette smoke.

When sufficient c-Jun levels are present, heterodimerization occurs and c-Jun and c-Fos combine, forming a complex of transcription factor activator protein 1. This complex induces matrix metalloproteinases (MMPs)—including collagenase, gelatinase, and stromelysin, which degrade the skin and connective tissue.

Fisher and colleagues\(^1\) reported the results of in vivo studies on human skin showing that retinoids prevent the upregulation of c-Jun. With insufficient amounts of c-Jun available to bind with c-Fos, transcription factor activator protein 1 cannot form and the pathway leading to the development of MMPs is blocked. Kang et al\(^2\) demonstrated that another pathway exists in this process, involving two other genes in the mitogen-activated protein (MAP) kinase family, ERK and JNK (Figure). ERK and JNK have the ability to upregulate both c-Jun and c-Fos expression. Thus, UV radiation upregulates the expression of c-Jun directly, but also upregulates the expression of ERK and JNK, which, in turn, upregulate the expression of c-Jun and c-Fos.

This discovery is important because it proves that free radicals (also known as reactive oxygen species) are involved in aging through the activation of ERK and JNK genes, which then activate c-Jun and c-Fos in the same pathway. This new information also supports the notion that photoaging can be prevented by blocking the production of reactive oxygen species. This can be accomplished by blocking activation of ERK and JNK through prevention of exposure to UV radiation with the use of antioxidants. In addition, Kang et al\(^2\) showed that the antioxidants genistein and N-acetyl cysteine interrupt the UV signaling cascade by blocking c-Jun activation. F’guer and colleagues\(^3\) also showed that antioxidants can prevent actions of the ERK and JNK genes. They demonstrated that keratinocytes pretreated with either the fraction of green tea known as epigallocatechin gallate (EGCG) or ascorbic acid and then irradiated with UV light showed diminished MAP kinase activity—and a decrease in both ERK and JNK activity.

**FOCUS ON PREVENTION**

Photoaging is manifested by the loss of three major elements in the skin: collagen, elastin, and glycosaminoglycans (hyaluronic acid). The photoaging pathway described above explains the loss of collagen: the formation of collagenase, which destroys collagen. Elastin and hyaluronic acid are broken down by elastase and hyaluronidase, respectively, but these pathways are less well characterized. It has been shown that young skin contains collagen fibers that are attached to elastic fibers by hyaluronic acid. The hyaluronic acid attachments are depleted in older skin, allowing the collagen and elastin fibers to become disorganized. It is believed that certain hyaluronic acid products (those that have the collagen and elastin binding sites still available) can be injected into the dermis, where they will form bonds with collagen and elastin. This should revert the
dermal collagen and elastin to the more youthful pattern.

Cosmetic dermatologists have excellent choices of dermal fillers (collagen and hyaluronic acid), to replace the lost collagen and glycosaminoglycans, respectively. In addition, a host of other procedures have been developed for repairing some of the consequences of photoaging. Nevertheless, as with all other health issues, prevention is always the preferred focus.

First, broad-spectrum sun protection against both UVA and UVB radiation is essential. My preference is an avobenzene-containing product to block UVA followed by a product containing zinc oxide or titanium dioxide. (Terephthalalidine dicamphor sulfonic acid is a superior UVA blocker, but it is found currently only in products imported from Europe.) Many makeup foundations contain sunscreens, but I caution patients to not rely on these and to always use a sunscreen-containing moisturizer or a sunscreen product. The iron oxide and other pigment molecules that give color to the makeup can degrade some of the UVA blockers, like avobenzene.

Patients should be advised to use a sufficient amount of sunscreen. Users of sunscreens only apply 25% of the amount that is considered adequate. Wearing sun-protective clothing while outdoors is an important adjunct to sunscreen use.

Second, oral antioxidant vitamins block the mechanism of sun damage described above. To date, it is not known whether topically applied antioxidants are stable and/or if they penetrate the skin to achieve the desired effect at the cellular level. Third, as noted, EGCG has been shown to prevent photodamage, so drinking green tea may be helpful in this regard.

Retinoids improve cosmetic appearance by smoothing fine wrinkles, but, as noted, retinoids also block the photoaging pathway by blocking activation of c-Jun and c-Fos. Patients who experience erythema or discomfort from retinoids typically also have dry skin. Therefore, a good moisturizing regimen should help with tolerance.

Finally, any patient who still smokes cigarettes should be educated about the skin damage associated with exposure to cigarette smoke.

TREATMENT OF ACTINIC KERATOSES IN COSMETICALLY SENSITIVE AREAS

Exposure to UV light damages the skin through other pathways as well, and these lead to the development of actinic keratoses (AKs), invasive squamous cell carcinoma (SCC), basal cell carcinoma, and melanoma. These mechanisms are described by Dr. Gaspari in his article, “Consequences of Photodamage: Actinic Keratosis Etiopathogenesis,” page 4. Dr. Spencer reviews the range of treatments currently available for AKs, page 6. AKs require treatment because of the risk for progression to invasive SCC. The treatment of AKs in cosmetically sensitive areas, specifically, will be briefly addressed here.

For most patients, the head and neck areas are those considered to be most cosmetically sensitive. However, depending on factors such as the patient’s occupation or simply his or her personal preference, other areas may also be cosmetically sensitive.

Cryosurgery is the most commonly used treatment for AKs, but the risk for hypopigmentation and scarring makes liquid nitrogen a problematic choice when cosmetic outcome is a concern. In addition, multiple AKs treated with cryosurgery may lead to multiple white spots. Appearance-sparing options include trichloroacetic acid (TCA) peels or spot TCA applications, 5-fluorouracil (5-FU), diclofenac, and imiquimod.

TCA is a treatment that sometimes is not covered by insurance, so this should be established and discussed with the patient. 5-FU and diclofenac are agents that are currently approved by the U.S. Food and Drug Administration for the treatment of AKs. When used daily, as is typically recommended, 5-FU usually causes a reaction that resembles a severe sunburn with flaking.

Phase III clinical trials with imiquimod have recently been completed, and publication of the results is expected during the winter of 2003 and 2004. The accumulated evidence published indicates that this immune response modifier is effective in clearing AKs and is associated with mild to moderate local skin reactions, including erythema, edema, and erosions. Patients who are given imiquimod therapy should be advised to expect these reactions and informed that the intensity of these effects can be reduced by decreasing the frequency of applications or taking rest periods from treatment. It appears that such a strategy has no adverse effect on efficacy, but this observation must be confirmed by further study. In our experience, treatment of actinic cheilitis with imiquimod requires less frequent dosing than three times weekly. We begin with once-or twice-weekly applications and titrate to tolerability.

CONCLUSION

It has become clear that collagen, elastin, and glycosaminoglycans are important elements that are lost in aged skin. Aging of the skin can be prevented by protecting these elements using antioxidants and retinoids and avoiding sun exposure and cigarette smoke. Once skin aging has occurred, therapy involves increasing levels of these elements using topical creams, mechanical agents, and injectable products. The current trend is toward the combined use of preventative and restorative strategies.

REFERENCES

Consequences of Photodamage: Actinic Keratosis Etiopathogenesis

Continued from page 5

bers of skin cancers occur in the elderly as a result of cumulative insults from years of UV exposure, as well as declining DNA repair defense mechanisms.

Conclusions

The perturbations of epidermal cells that occur with a single episode of UV light exposure have been shown to be reversible. The regression of AKs in human subjects that has been reported episode of UV light exposure have been shown to be reversible. It has been demonstrated that, with chronic UV light exposure over a period of years, more profound changes occur, including carcinogenesis resulting from genetic mutations in keratinocytes as well as defects in the immune system.

References

17. Rivaz JM, Ulrich SE. The role of IL-4, IL-10, and TNF-α in the immune suppression induced by ultraviolet radiation. J Leukocyte Biol. 1994;56:769-775.
Skin & Allergy News®

Improving Medical and Cosmetic Outcomes in Actinic Keratoses

CME Post-Test and Evaluation

SKIN & ALLERGY NEWS certifies that this educational activity has been recognized for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology’s Continuing Medical Education Award.

There is no fee to participate in this activity. If you wish to receive CME credit, please mail or fax a photocopy of this completed form before December 2004 to:

Course No. 281-100 Dermatology, SKIN & ALLERGY NEWS
60 Columbia Road, Bldg. B, Morristown, NJ 07960-4526 • (973) 290-8200 • (973) 290-8245 Fax

INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Circle the most appropriate response.

Seven correct responses are required for credit.

1. Destructive therapy also considered to be a method of field therapy is:
   a. Cryosurgery
   b. Imiquimod
   c. Photodynamic therapy
   d. Resurfacing procedures

2. The greatest adverse effects on the skin have been associated with ultraviolet (UV) light:
   a. From tanning salons
   b. In the range of 320 to 400 nm (UVA)
   c. In the range of 290 to 320 nm (UVB)
   d. In the range of 200 to 290 nm (UVC)

3. Which one of the following statements describes evidence derived from studies of imiquimod in the treatment of patients with actinic keratoses?
   a. Persistent inflammation following the cessation of imiquimod applications should be treated with topical corticosteroids.
   b. Severe side effects are uncommon.
   c. Reducing the frequency of applications also reduces efficacy.
   d. Subclinical lesions are unaffected.

4. The gene considered to be the “guardian of the genome” is:
   a. c-Jun
   b. JNK
   c. Ki-67
   d. p53

5. The Langerhans’ cells that survive direct damage from ultraviolet (UV) light are exposed to a number of soluble immunosuppressive mediators that are derived from:
   a. Epidermal keratinocytes
   b. Oncogenes
   c. Survivin
   d. Telomerase

6. The central cell type affected by ultraviolet light is the:
   a. Langerhans’ cell
   b. Helper T cell type 2
   c. Helper T cell type 1
   d. Suppressor T cell

7. The gene c-Fos combines with ___ to form transcription factor activator protein 1.
   a. c-Jun
   b. ERK
   c. JNK
   d. Retinoids

8. The photoaging pathway that involves c-Jun, c-Fos, ERK, and JNK explains the loss of:
   a. Collagen
   b. Elastin
   c. Glycosaminoglycans
   d. Hyaluronic acid

9. Which one of the following statements is true concerning the destruction of actinic keratoses (AKs) by liquid nitrogen?
   a. AKs are destroyed on brief exposure to liquid nitrogen—between 1 and 3 seconds.
   b. AKs are destroyed only when depth of freeze is at least 0.3 to 0.4 mm.
   c. Creation of a vesicle is required for cryotherapy to be effective.
   d. Cryosurgery is useful as a “field therapy” for AKs.

10. The development of a large area of squamous cell carcinoma arising from confluent actinic keratoses (AKs) is a phenomenon referred to as:
    a. AK progression
    b. Field cancerization
    c. Keratinocyte intraepithelial neoplasia continuum
    d. Treatment failure

EVALUATION FORM: We would appreciate your answering the following questions in order to help us plan for other activities of this type.

Name ___________________________ Specialty ___________________________
Address ___________________________ City __________________ State ______ ZIP ______
Phone __________________ Fax __________________
Signature __________________ E-mail __________________

1. How would you rate the clarity of the presentation of the material? (Please check.)
   Text ______ ______ ______ ______
   Photographic Images ______ ______ ______ ______
   Post-Test ______ ______ ______ ______

2. How would you rate the clinical relevance of the material? ______ ______ ______ ______

3. How would you rate this material, compared with similar independent study presentations in print format? ______ ______ ______ ______

4. Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

5. Do you believe such materials, supported by educational grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful).

6. What topics would you find useful for future programs?

7. Other comments:

Copyright 2004 INTERNATIONAL MEDICAL NEWS GROUP, AN ELSEVIER COMPANY